Pre-mortem Diagnosis of Sporadic Creutzfeldt-Jakob Disease in Practice

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Abstract

We describe a case of Sporadic Creutzfeldt-Jakob disease (sCJD) and discuss our evidence-based diagnostic process.

Key Clinical Message

Sporadic Creutzfeldt-Jakob Disease (sCJD) should be considered in any case of rapid neuropsychiatric decline. While real time quaking induced conversion (RT- QuIC) tests have simplified premortem diagnosis of probable sCJD, neuropathological examination of a brain biopsy specimen remains the only method of definitive diagnosis. Exclusion of reversible disease is imperative.

Introduction

Prion diseases are caused by the neurotoxic accumulation of misfolded prion protein. Accumulation or "seeding" occurs exponentially as misfolded prion protein induces normal cellular prion protein to misfold[1,2]. Sporadic Creutzfeldt-Jakob Disease (sCJD) accounts for the vast majority of prion disease cases but is rare, occurring in approximately 1 in 1 million per year worldwide[3]. The clinical syndrome associated with sCJD is characterised by rapid neuropsychiatric decline leading to akinetic mutism and death within one year of symptom onset[4]. There are no curative treatments available.

We describe a case that presented with multiple neuropsychiatric and neurological symptoms that could not be localised to one anatomical region. We describe the process by which we

diagnosed him with probable sCJD. We discuss the evidence base for diagnostic tools we used with reference to the 2018 Centers for Disease Control and Prevention (CDC) diagnostic criteria for sCJD[5] (Figure 1).

Case Description

A 70 year old previously independent man presented to a regional emergency department with a one-month history of progressive unsteadiness on his feet. At the time of presentation, he required support just to stand. He also described episodes of diplopia, lasting 3-4 minutes and resolving spontaneously 1-2 times per day. Recent review by an optometrist had been unremarkable. On enquiry the patient and his wife also admitted he had experienced recent memory impairment and significant behavioural changes. These included hyperphagia, emotional lability and impulsivity, consistent with frontal lobe syndrome. Of significance, the patient was treated for an ear infection two weeks prior to symptom onset, however he denied vertigo, nausea or vomiting. He also denied headaches, neck stiffness or photophobia. He had worked with meat for most of his life but had never been overseas. He did not have incontinence to suggest Normal Pressure Hydrocephalus. He denied any upper limb incoordination. He had not consumed alcohol for 34 years. His father had been diagnosed with Parkinson's Disease at age 68 but he had no other family history of neurological disease.

On examination, he had a severely ataxic gait. Romberg's test was negative and evidenced severe truncal ataxia. The patient required support from the examiner to stand with eyes open. Despite denying any difficulty utilising his upper limbs, he had bilateral dysdiadokinesis and dysmetria. He also had mild rigidity in his upper limbs and was globally hyporeflexic. Glabellar tap test was positive. There was no clonus. Full power was preserved throughout all four limbs. Sensation including proprioception and vibration sense was also preserved.

Cranial nerve examination was unremarkable. While the patient was oriented, able to follow three stage commands and behaviourally appropriate during examination, further bedside cognitive testing revealed subtle impairments. The patient failed serial seven subtraction testing despite repeated instructions. He recalled only one out of three objects after five minutes, even after prompting with a choice of three objects for each he couldn't recall. On a clock-drawing test, he failed to set the time to "ten past five", instead leaving marks next to the numbers 10, 2 and 5 after much deliberation.

In summary, our patient presented with rapidly progressive ataxia, intermittent diplopia and new cognitive and behavioural disturbance. There were both cerebellar and extrapyramidal signs on examination. Given the patient's vascular risk factors including Ischaemic Heart Disease, Type 2 Diabetes Mellitus, Hypertension and Hypercholesterolaemia, an ischaemic event was considered but thought inconsistent with the gradual onset of ataxia and diversity of additional symptoms. Given a history of prostate cancer and skin melanoma, a paraneoplastic etiology was initially strongly favoured. Other differential diagnoses included atypical infection, autoimmune disease, toxicity, metabolic derangement and prion disease.

Blood tests were unremarkable. Creatinine, liver enzymes, blood sugar level, electrolytes and thyroid function were normal. Vitamin B12 and folate were replete. Inflammatory markers were not elevated. Cryptococcus, Toxoplasma, HIV and Syphillis serologies were negative. ANA, ENA and anti-dsDNA were normal. Anti-neuronal, anti-VGKC, anti-LG-1, anti-Caspr-2, anti-GQ-1, anti-GM-1 and anti-GAD antibodies were not detected. Copper and ceruloplasmin levels were also normal. Initial tests on cerebrospinal fluid (CSF) were equally unremarkable. Opening pressure was at the upper limit of normal (20 cmH_20). Biochemistry was bland. Gram stain showed no bacteria and culture was negative. Cytology showed no

features of malignancy. Herpes and Enterovirus PCR were negative. Anti-neuronal, anti-NMDA, anti-GABA and anti-AMPAR antibodies were not detected. A computed tomography (CT) non-contrast scan of the brain performed in the emergency department was unremarkable. A CT of the chest, abdomen and pelvis showed no evidence of malignancy.

Our patient was admitted and treated empirically with 300mg intravenous thiamine thrice daily while awaiting further diagnostic work-up. A magnetic resonance imaging (MRI) scan with T2-weighted, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences was obtained. When this showed new symmetric hyperintensity in the basal ganglia as well as subtle hyperintensity of the insular cortex and frontal cortical rim (Figure 2), further investigations to support prion disease were pursued. Electroencephalography (EEG) was normal. The CSF was positive for 14-3-3 protein and total Tau protein was also elevated with a concentration of 5,714 pg/ml. Importantly, a RT-QuIC test performed on CSF was positive, strongly suggesting a diagnosis of sCJD. Before these results were returned, pulsed methylprednisolone was trialed for three days without effect. The patient returned home to receive palliative care and his symptoms progressed rapidly. He died approximately three months after symptom onset. The results of a post-mortem examination eventually revealed a spongiform encephalopathy associated with neuronal loss, gliosis and a synaptic pattern of prion protein immunoreactivity. Changes were most marked in the cerebellum.

Discussion

The presence of neuropsychiatric disorder is a consistent feature of sCJD and required for its premortem diagnosis[5] (Figure 1). Progression is classically rapid, helping to distinguish it from other forms of dementia. However, features of the neuropsychiatric disorder are highly

heterogeneous. Deficits may include memory loss, impaired attention, frontal lobe syndrome, aphasia, apraxia[6], psychotic symptoms and mood disorder[7]. Behavioural symptoms have been observed to fluctuate[7].

Associated neurological symptoms are equally heterogeneous. They commonly include ataxia and myoclonus, which is classically provoked by startle. Corticospinal tract involvement, extrapyramidal symptoms, sleep disturbance and visual symptoms are also well-recognised[8,9,10]. The range of possible visual signs and symptoms of CJD is extremely diverse. Blurred vision, diplopia, various patterns of visual field loss, cortical blindness, palinopsia, supranuclear palsies, nystagmus, saccadic abnormalities, impaired smooth pursuit, failure of convergence and abnormal vestibulo-ocular reflex have all been reported. The diplopia described by our patient is among the most frequently reported visual symptoms and may be intermittent[9].

The myriad of possible signs and symptoms generates a spectrum of presentations of sCJD. As the rarity of the disease limits clinicians' exposure to it, if classical symptoms are missing or obscured by lesser known ones the diagnosis may not be considered. Profound cognitive impairment may also limit history, examination and investigative procedures that might have illuminated the diagnosis. Accordingly, it is not uncommon for the diagnosis to be missed or delayed[11].

In our case, early neuropsychiatric symptoms were overshadowed by more overt neurological symptoms. The patient's primary complaint had been his debilitating ataxia. Only on purposeful enquiry and with assistance from his wife was a simultaneous neuropsychiatric decline revealed. In other cases, psychiatric symptoms have been more prominent and

patients have presented initially to mental health services[12]. The breadth of our patient's deficits, elicited by thorough history and examination, reflected abnormal function in neuroanatomically disparate regions and rendered our initial differential diagnoses and investigations appropriately broad.

Careful exploration of differential diagnoses is essential because definitive diagnosis of sCJD can only be made on neuropathological examination of a brain biopsy specimen[5], usually performed post-mortem due to risk of iatrogenic transmission. The importance of thorough initial investigations is illustrated by a retrospective review of brain autopsies referred to US National Prion Disease Pathology Centre between 2006 and 2009. Of 1,106 cases referred with a suspected diagnosis of prion disease, 352 did not show pathological features consistent with the diagnosis. Of note, the most common diseases misdiagnosed as prion diseases were Alzheimer's Disease and Vascular Dementia, which may progress more quickly than is typical. However, most concerning is that 71 cases showed features of treatable disease. These included a variety of immune-mediated, neoplastic and infectious diseases as well as three cases of Wernicke's Encephalopathy[13]. In addition to causing premature withdrawal of care, unwarranted suspicion of prion disease may limit diagnostic options including brain biopsy and place unnecessary emotional burden on family members. Similarly to the presence of a neuropsychiatric disorder, exclusion of reversible causes is integral to premortem diagnosis of sCJD[5] (Figure 1).

Until the development of FLAIR and DWI MRI sequences, supplements to history and examination to support the diagnosis of sCJD in a living patient were limited to suggestive EEG and non-specific markers of neuronal injury in the CSF. The classic EEG finding of periodic sharp wave complexes (PSWCs) occurs in approximately two thirds of patients

during the course of illness[14,15,16] and is up to 91% specific for CJD[15]. However, a positive result is significantly less likely in the early stage of clinical disease than the final stage[16]. The sensitivity of elevated CSF protein 14-3-3 appears to be less variable across stages of disease[16]. A systematic review showed that elevated 14-3-3 has a sensitivity of 92% and a specificity of 80% for a diagnosis of sCJD[17]. Diseases that are most likely to produce false positives are readily clinically distinguishable from sCJD[8]. However, important differential diagnoses for sCJD including other forms of dementia and encephalitis have been associated with elevated 14-3-3[8,18]. CSF protein Tau appears to have similar sensitivity and specificity to 14-3-3[8] and elevation of both may enhance diagnostic accuracy[19] but Tau has not been incorporated into diagnostic criteria.

MRI changes associated with sCJD have been reported to precede the onset of significant symptoms[20,21]. The characteristic changes are bilateral hyperintense signal in the basal ganglia and the rim of the cerebral cortex. The basal ganglia changes preferentially affect the caudate and putamen and are usually but not always symmetrical. The cortical changes typically spare the peri-rolandic area and are known as "cortical ribboning"[22]. Signal intensity progresses with disease[23]. Remarkably, the changes spare the cerebellum even when there are clear cerebellar signs on assessment by an experienced neurologist[24]. Cortical atrophy is seen in end-stage disease[25]. DWI is most sensitive, followed by FLAIR and T2 sequences[25,26]. Sensitivity for sCJD is shown to be 95% or more in some studies[27,28,29]. It also has the fortunate advantage of being the quickest sequence to obtain, minimising motion artefacts in demented patients who may not tolerate stillness[31] or indeed other investigations.

Of note, inter-rater variability of identification of characteristic MRI changes is high[31]. Cortical changes are often missed[32]. In our patient's case, cortical changes were subtle

(Figure 2), only evident on DWI and appreciated only with the benefit of hindsight. Characteristic changes are also non-specific[22] and need to be interpreted in the context of the whole clinical picture. Such changes should be actively sought when the diagnosis is considered. Any of characteristic MRI changes, elevation of 14-3-3 in CSF or PSWCs on EEG make the diagnosis of sCJD probable when it occurs in the setting of rapid neuropsychiatric decline and typical neurological symptoms[5] (Figure 1).

Recent development of the RT- QuIC test[33] has further facilitated diagnosis of sCJD. In this test, a sample of cerebrospinal fluid is added to a mixture of recombinant prion protein and fluorescent dye. Any misfolded prion protein in the cerebrospinal fluid will induce misfolding of the recombinant prion protein and result in accumulation of polymers, a process hastened by shaking of the mixture. Dye binds the polymers, such that their gradual accumulation will result in a gradual increase in fluorescence. In effect, the test confirms prion seeding activity from which the presence of misfolded prion protein in the CSF can be inferred. It is 96% sensitive and 100% specific for sporadic CJD[34]. Accordingly, a positive RT-QuIC test in association with neuropsychiatric decline makes the diagnosis of sCJD probable[5] (Figure 1). However, this remains a novel test for a rare disease. In our case, due to limited testing capacity in Australia the result did not become available until after the patient's death.

Even without the RT-QuIC test result, our patient met diagnostic criteria for probable sCJD (Figure 1). He evidenced rapid neuropsychiatric decline. Investigations for reversible infectious, autoimmune, paraneoplastic and metabolic causes were negative, including non-response to empirical treatments for Wernicke's Encephalopathy and inflammatory processes. He had visual symptoms as well as both cerebellar and extrapyramidal signs at the

time of presentation. A sample of his CSF was positive for 14-3-3 protein and total tau protein was also elevated. MRI showed high signal in the caudate and putamen bilaterally. Early pursuit of the diagnosis simultaneously with more expansive investigations led to early referral to and benefit from palliative care services.

Post-mortem neuropathology eventually confirmed CJD. It should be noted that rare genetic forms of CJD may resemble sCJD both clinically and pathologically. Sporadic and genetic forms can only be clearly distinguished with genetic testing. In the absence of a positive family history of the disease, this case is very likely to have been sporadic.

Conclusions

The pre-mortem diagnosis of probable sCJD is challenging. Classical signs and symptoms may not be prominent during early disease or may be disguised by lesser known ones. Clinicians should think of the diagnosis whenever the cardinal feature of rapid neuropsychiatric decline is noted. Prompt consideration is necessary to facilitate timely end-of-life care. Performance of investigations and return of results may scarcely keep pace with progression of disease.

While EEG and CSF proteins 14-3-3 and Tau remain valuable tools to support the diagnosis, development of DWI has yielded a highly sensitive imaging method. Careful evaluation can reveal changes in very early disease, though they are non-specific. The RT-QuIC test is a pivotal discovery. Its high specificity simplifies pre-mortem diagnosis of probable sCJD. However, exclusion of reversible disease remains essential. Clinicians should take care not to prematurely narrow the focus of their investigations.

Figure Legends

Figure 1: 2018 Centers for Disease Control and Prevention (CDC) diagnostic criteria for Sporadic Creutzfeldt-Jakob Disease[5]

Figure 2: Axial diffusion weighted magnetic resonance images demonstrating hyperintensity of the caudate nucleus (blue arrows), putamen (green arrows), frontal cortical rim (red arrows) (left), body of the caudate nucleus (yellow arrows) and insular cortex (purple arrow) (right) approximately five weeks after symptom onset.

Author Contributions

Dr Elina T Ziukelis: Conception and design, acquisition and analysis of data, drafting of the manuscript

Dr James J Gome: Conception and design, acquisition and analysis of data, revision of the manuscript

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